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Original Article

Formulation, Optimization and *in vitro* Evaluation of Ibuprofen-Loaded Cubosomal Nano-Formulation for Effective Topical Delivery

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ABSTRACT

Objectives: This research aims to formulate and assess an Ibuprofen-loaded cubosomal gel that would improve the drug's skin absorption and minimize its oral adverse effects. Hence, clinically relevant drug concentration reaches the skin surface for effective transdermal delivery. **Materials and Methods:** Ibuprofen-loaded Cubosomal Nanoformulation was prepared using a top-down approach by varying Glyceryl Mono-Oleate (GMO) and Polaxomer 407 (PF 127). The prepared cubosomal nanoformulations were subjected to characterization such as Poly Dispersibility Index, Particle Size and Entrapment Efficiency. The optimized formulation of Ibuprofen-loaded Cubosomes was incorporated in Carbopol 940 (1%) gel base. The gel formulations were evaluated for pH, viscosity, spreadability, *in vitro* drug diffusion through a cellophane membrane and *ex vivo* diffusion studies using rat skin. **Results:** A 3^2 factorial design was utilized for formulation optimization. The optimized cubosomal nanoformulation (F5) produced particles with an average particle size of 150.7 nm and PDI of <1, zeta potential of -29mV and %drug entrapment efficiency of 74.36±0.66%. The formulated Cubosomal Gel revealed a neutral pH value with a viscosity of 1123±0.45cps, 75% *in vitro* drug diffusion and 78.6% *ex vivo* drug diffusion. **Conclusion:** pH, viscosity, spreadability, drug release and stability studies were performed on the Cubosomal gel formulation. The optimized Formulation (F5) performed better in terms of pH, viscosity, spreadability and drug release percentage. *In vitro* and *ex vivo* studies shows that Ibuprofen-loaded Cubosomal gel releases the drug more slowly than plain formulated Ibuprofen Gel. The formulated Cubosomal Gel also showed no significant change in physical characteristics. Hence, concluded that the formulated Cubosomal gel can be used as an effective transdermal drug delivery system.

Keywords: Cubosomes, Ibuprofen, Nano-formulation, Transdermal drug delivery.

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INTRODUCTION

Ibuprofen is common non-steroidal anti-inflammatory drug, also known as NSAID are used to treat fever, acute pain, swelling and stiffness alone or in combination with caffeine or Paracetamol.[1,2] It is effective for the general treatment of the autoimmune disorder, degenerative joint disease and redness.[3] Ibuprofen's function in prescription drugs is limited due to a variety of issues, including its low liquid solubility, quick systemic clearance (blood plasma half-life is 1.8 hr), insufficient tissue absorption, as well as poor bioavailability.[4]

Uncertainty surrounds the precise mode of action of ibuprofen. Ibuprofen, on the other hand, inhibits an enzyme called cyclooxygenase, via the arachidonic acid pathway, responsible for the production of chemical messengers (prostaglandins) and thromboxanes (blood clotting stimulators).[5] It inhibits both COX-1 and COX-2 activity. COX-1 inhibition is speculated to be the root cause of some ibuprofen adverse effects, such as gastrointestinal ulcers while, COX-2 inhibition reduces the synthesis of prostaglandins that are involved in regulating swelling, fever, discomfort, inflammation and oedema.[6] Oral administration of Ibuprofen causes gastrointestinal issues like stomachic discomfort, nausea and vomiting, thereby reducing patient compliance.[4,7] Transdermal administration of Ibuprofen, prevents the aforesaid facet effects, improves adherence among patients and maintains drug levels in the blood for a longer duration of time.[8]

Transdermal drug delivery is an effective way of delivering drugs to the circulatory system via the surface layers of the skin.[9] Because of their tremendous benefits over conventional delivery systems; transdermal drug delivery methods continue to

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captivate the interest of researchers.[10] This is owing to its capacity to transport various medications into the bloodstream, eliminate liver first-pass metabolism and boost patient adherence.[11] Since Ibuprofen is lipophilic in nature, cubosomes, liposomes, nanoparticles, etc., can be employed as transdermal delivery methods to administer the medication successfully. These transdermal systems permit sustained or controlled release of standard medicines.[12,13]

Cubosomes are liquid crystalline particles that self-assemble from surfactants and have solid-like rheology and the right water-to-microstructure ratio.[14,15] The huge internal as well as external surface area per unit volume of this structure makes it an excellent drug delivery mechanism. For loading more hydrophobic medications and enabling longer release, the cubosome system is seen to be a desirable option.[16]

Therefore, the goal of the current study was to formulate and assess an Ibuprofen-loaded cubosomal gel that would improve medicine absorption through the skin and reduce oral adverse effects while still being secure and reliable. Ibuprofen-loaded cubosomal gel that would increase medication absorption through the skin and minimize oral side effects while remaining safe and effective.

MATERIALS AND METHODS

Mohini Organics Pvt. Ltd., of Mumbai, India supplied glyceryl monooleate. A sufficient sample of Poloxamer 407 was supplied from Sigma Aldrich. Ibuprofen was purchased from one amongst the API vendors. All different ingredients utilized were of analytical grade.

Methods

Experimental Design

In this study, a 3^2 factorial design was applied to analytically optimize certain variables for the development of Ibuprofen-loaded Cubosomes. Two independent variables each at 3 levels, namely GMO(X_1) and PF127(X_2) concentrations were evaluated for their effects on the dependent variables i.e., cubosomal %Entrapment efficiency (Y_1) and the mean particle size (Y_2) of Ibuprofen-loaded cubosomes (Table 1).

The effect of independent variables X1 and X2 on the properties of Ibuprofen-loaded cubosomes (Y1 and Y2) was investigated in order to achieve Ibuprofen-loaded cubosomes with the smallest particle size and the highest entrapment efficiency.

Preparation of Ibuprofen-loaded Cubosomal nanoformulation

Ibuprofen cubosomal nanoformulation was prepared using a top-down approach.[17] Various concentrations of GMO and PF 127 were precisely measured and melted individually in an electric water bath kept at 70°C. To the molten GMO, the drug was added and heated until completely dissolved. The drug-GMO mixture was more to an aqueous polymer solution (poloxamer 407). The resulting mixture was added slowly to deionized water dropwise. The mixture was homogenized for 15 min using a Homogenizer (IKA T18 digital ultra Turax) at 15000 revolutions per minute and further probe sonicated (Ultrasonic probe sonicator VC750) for 5 min. The final solution produced was a white opaque mixture with no clumps or particles. The developed cubosomal nanoformulation was preserved in closed amber-coloured glass tubes for 72 hr before being evaluated. The basic compositions of all possible solutions for formulating Ibuprofen-loaded cubosomes are shown in Table 2.

Characterization of Ibuprofen loaded Cubosomal dispersion

Visual inspection

All prepared formulations were visually evaluated for color, consistency, the presence of any agglomerates and particle material deposition on the surface of glass bottles, referred to as "ring formation."[18]

Determination of Zeta Potential and Particle size

The particle size, distribution and zeta potential of the cubosomal nanoformulation were assessed using Dynamic Light Scattering and Zetasizer. Samples were analyzed in triplicate at 25±0.5°C after being diluted (100-fold) in deionized water.[19]

Determination of drug content

1 mL of Ibuprofen-loaded cubosomal mixture was dissolved in 25 mL of Methanol (HPLC Grade).[20,21] To get a clear solution, the dispersion was stirred continuously for 10 to 15 min. The concentration of Ibuprofen in methanol was determined spectrophotometrically at λ_{max} 225 nm.[22] From the equation given below, drug content can be calculated:

$$Drug\ Content = \frac{Actual\ yield}{Theoretical\ yield} \times 100$$

Entrapment efficiency

Ultrafiltration centrifugation was used to determine the entrapment efficiency. In Eppendorf tubes, 2 mL of freshly made Ibuprofen-loaded cubosomal dispersion were filled before 15 min of centrifugation at 4°C and 13500 rpm. The obtained solution was partitioned, and the supernatant liquid was recovered. The recovered liquid was adequately diluted and the entrapped drug was determined using UV-vis Spectrophotometer at 266 nm.[22,23] According to the following equation, the %EE was calculated:

$$EE\% = \frac{Total\ drug - free\ drug}{Total\ drug} \times 100$$

Table 1: Dependent and independent variables of 3^2 factorial designs for the formulation of Ibuprofen-loaded cubosomes.

Factors (Independent Variables)	Levels		
	Low (-1)	Intermediate (0)	High (+1)
X_1: Concentration of GMO (%)	1	1.5	2
X_2: PF 127 concentration (%)	5	7	9
Responses (Dependent variables)	Units		Goal
Y_1: Entrapment Efficiency	%		Maximum
Y_2: Average particle size	Nanometer (nm)		Minimum

Table 2: Composition of Ibuprofen loaded cubosome.

Formulation	Drug (Ibuprofen)	Glyceryl mono-oleate (GMO)	Polaxomer 407	Water (%)
F1	50 mg	5%	1%	94%
F2	50 mg	7%	1%	92%
F3	50 mg	9%	1%	90%
F4	50 mg	5%	1.5%	93.5%
F5	50 mg	7%	1.5%	91.5%
F6	50 mg	9%	1.5%	89.5%
F7	50 mg	5%	2%	93%
F8	50 mg	7%	2%	91%
F9	50 mg	9%	2%	89%

In vitro drug release

A dynamic dialysis method was employed for assessing the *in vitro* release of ibuprofen from cubosomes.[24] To determine the drug release rate after separating the free drug from drug-loaded cubosomes, the cubosomal nanoformulation was put in dialysis tubing and completely filtered for 15 min multiple times, repeatedly against 100 mL of pH 7.4 phosphate buffer. After 1 hr, free Ibuprofen had been completely removed from the solution and no more medication was present. Ibuprofen-loaded cubosomes or a simple drug aqueous solution were dialyzed and then placed in a dialysis bag. After that, the dialysis bag was submerged in 100 mL of phosphate buffer (pH 7.4) that had been thermostatically heated to 37.5°C and magnetically swirled at 50 rpm. After withdrawing 1 mL of sample at various periods and measuring it with a UV spectrophotometer at 266 nm, the compartment was replaced with an equivalent volume of phosphate buffer (7.4). The experiments were carried out in threes.

Morphological Evaluation of Cubosomes (TEM Analysis)

The morphology of cubosomes was examined using a Field Emission Gun Transmission Electron Microscope 120/200 Kv set to 200 Kv.[25]

Selection of optimized batch

The optimized cubosome batch was selected from the nine cubosomal formulations based on the requirement of maximum entrapment efficiency and the lowest particle size. The F5 batch with poloxamer 407 (1.5% w/w) GMO (7% w/w) concentrations were chosen for additional evaluation investigations due to maximum %EE (74.36%) and smaller particle size (150.8 nm) based on the results obtained for dependent variables. The optimized cubosome batch F5 was used for formulating Cubosomal Gel.

Formulation of Ibuprofen loaded Cubosomal Gel

The optimized formulation of Ibuprofen-loaded Cubosomes (F5) was incorporated in Carbopol 940(1%) gel base. The formulated gels were assessed for viscosity, drug content, pH, *in vitro* drug diffusion via cellophane membrane and *ex vivo* diffusion studies using rat skin.

Evaluation of Ibuprofen-loaded cubosomal topical gel

Measurement of pH

A digital pH meter was used to measure the pH of the cubosomal gel. This was achieved by properly dipping the electrode in each solution and stabilizing it for 5 min.[26]

Viscosity

Using a Brookfield viscometer with a spindle number of 64, the viscosity of the optimized formulation was measured. The viscosity was measured in cps and the speed was steadily raised from 10-100 rpm.[24]

Determination of Drug Content

1 g of the prepared gel was combined with 100 mL of an appropriate solvent. After filtering the stock solution, aliquots of various concentrations were prepared and analyzed with a UV visible spectrophotometer at 266 nm.[27]

In vitro Drug Diffusion study

The Franz Diffusion Cell was utilized to conduct an *in vitro* skin diffusion/permeation study. A synthetic cellophane membrane served as the barrier separating the donor and receptor compartments of the Franz diffusion cell. In the donor part, 1 g of ibuprofen-loaded cubosomal gel was deposited, while the receptor portion was filled with pH 7.4 phosphate buffer. The diffusion cell was connected to a magnetic stirrer and the fluid in the receptor cell was thoroughly mixed using a magnetic bead at 50 rpm. A constant temperature of 37±0.5°C was maintained. In order to maintain the equilibrium state, the receptor compartment was replaced with an equivalent volume of phosphate buffer 7.4 each time the samples of 1 mL were removed at intervals of 30 min, 60 min, 90 min, 120 min, 4, 6, 8 and 10 hr. The removed samples were spectrophotometrically examined for drug content.[28]

Ex vivo Drug Diffusion Study

The Franz Diffusion Cell was utilized in an *ex vivo* skin permeation study. The skin from an excised rat abdominal skin was put between the diffusion cell's donor and receptor compartments. Ibuprofen-loaded cubosomal gel weighing 1 g was added to the donor compartment while the receptor compartment received phosphate buffer (pH 7.4). The diffusion cell was attached to a magnetic stirrer and the solution in the receptor cell was continuously mixed thoroughly at 50 rpm using a magnetic bead. A constant temperature of 37±0.5°C was maintained. In order to maintain the equilibrium state, the receptor compartment was replaced with an equivalent volume of phosphate buffer 7.4 each time the samples of 1 mL were removed at intervals of 30 min, 60 min, 90 min, 120 min, 4, 6, 8 and 10 hr. The removed samples were spectrophotometrically examined for drug content.[28]

RESULTS AND DISCUSSION

Evaluation of Ibuprofen-loaded cubosomes

Visual Inspection

There were no clumps or particle aggregates to be seen in any of the manufactured cubosomal formulations, which all displayed a homogeneous white milky appearance and were physically stable. Because PF 127, a superb stabilizing agent, is present, these formulations tend to be homogeneous. As a result of reducing particle fusion, poloxamer 407 reduces the formation of aggregates.

Determination of Particle Size, PDI and Zeta Potential of Cubosomes

The particle sizes of the cubosomal Formulations (F1-F9) were found to be ranging between 121.33±2.20 nm to 187.47±2.15 nm and PDI was found to be in the range of 0.11±0.02 to 0.57±0.04 (Table 3).

The Zeta potential of the cubosomal nanoformulations was reported to be between -11±0.07 to -36±0.12 (Table 3). Because of the extent of repulsive forces between adjacent, equally charged particles, particle aggregation is less likely in dispersion with a high zeta potential. Negative zeta potential formulations have high stability and dispersion quality.

Determination of drug content

As stated in Table 3, the drug content of the cubosomal dispersions (F1-F9) ranged from 86.00±0.02% to 106.50±0.05%.

Table 3: The characterized parameters of Ibuprofen loaded Cubosomes.

Formulation	Average Particle Size (nm)	PDI	Zeta Potential (mV)	% Drug Content (%)	Entrapment Efficiency (%)
F1	121.33±2.20	0.12±0.01	-18	98.24±0.23	51.29±0.35
F2	137.84±3.48	0.34±0.02	-25	86.24±0.02	54.76±0.63
F3	141.67±6.28	0.64±0.06	-36	102.3±1.12	60.08±3.34
F4	146.89±2.06	0.11±0.011	-15	99.56±0.72	72.96±0.51
F5	150.7±3.88	0.11±0.015	-29	101.2±1.22	74.36±0.66
F6	152.91±3.01	0.27±0.015	-11	92.56±0.71	79.83±0.473
F7	161.73±2.56	0.42±0.032	-17	90.91±1.01	81.79±0.55
F8	179.47±2.71	0.22±0.032	-24	95.45±0.88	84.64±0.34
F9	187.47±2.15	0.57±0.042	-23	106.5±0.05	87.55±0.591

Entrapment efficiency

Table 3 shows that the EE% of the produced Ibuprofen-loaded cubosomes ranged from 51.29±0.35% to 87.55±0.591%. Ibuprofen was successfully entrapped within cubosomes, revealing cubosome's potential as a promising lipid-soluble drug delivery method.

In vitro drug release

The cumulative drug release (Figure 1) from Ibuprofen-loaded cubosomal dispersion was found to be in the range of 88.72±1.37 after a period of 10 hr.

Surface Morphology

Figure 2 shows a negative stain transmission electron microscopy snapshot of cubic nanostructures scattered as individual particles.

Evaluation of Ibuprofen cubosomal topical gel

Determination of pH of Cubosomal Gel

The pH of the manufactured cubosomal gel (F5) was determined with the goal of ensuring that when applied topically, it did not influence the skin's pH and did not irritate it. The pH was determined to be 4.78±0.19.

Viscosity

The optimized formulation F5 showed an average viscosity of 1122±10.81 cps.

Drug content

The concentration of the drug in the optimized formulation F5 was reported to be 94.14±0.81%.

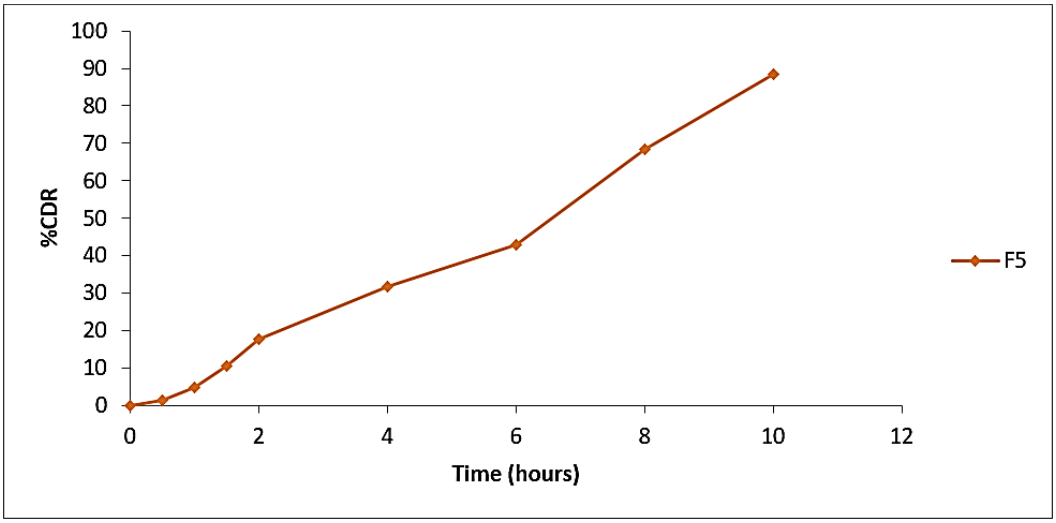

Figure 1: Release profile of Ibuprofen from optimized cubosomal dispersion.

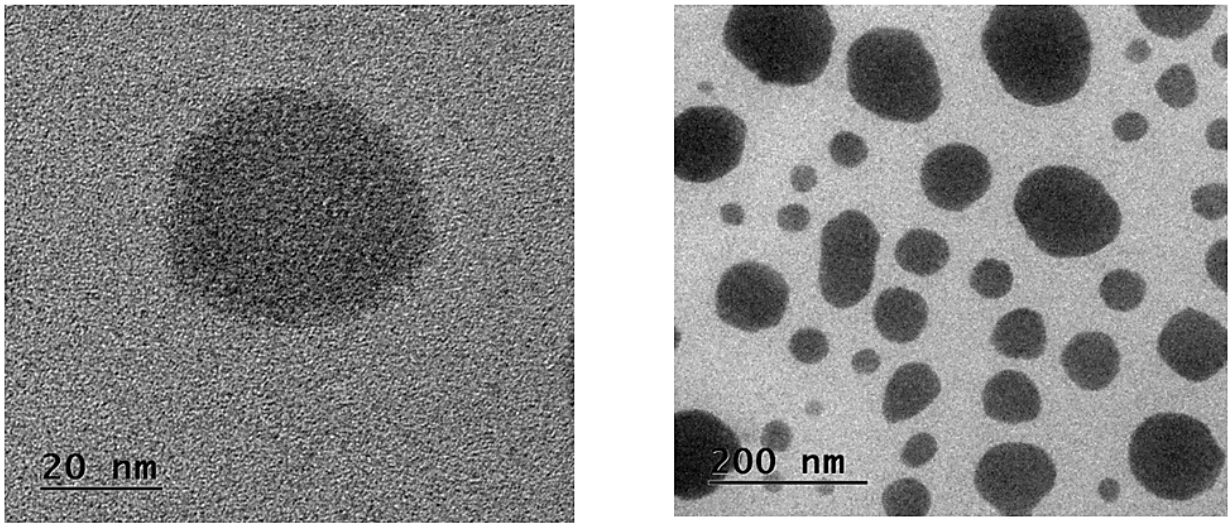

Figure 2: TEM Images of Optimized Formulation.

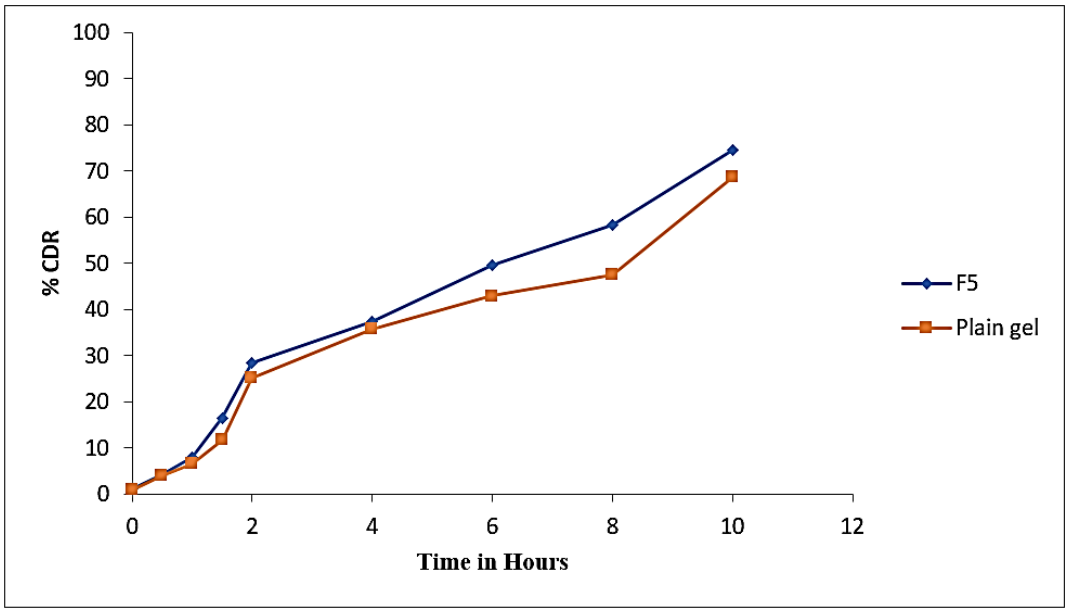

Figure 3: *In vitro* Diffusion of Plain Gel and Ibuprofen-loaded Cubosomal Gel (F5).

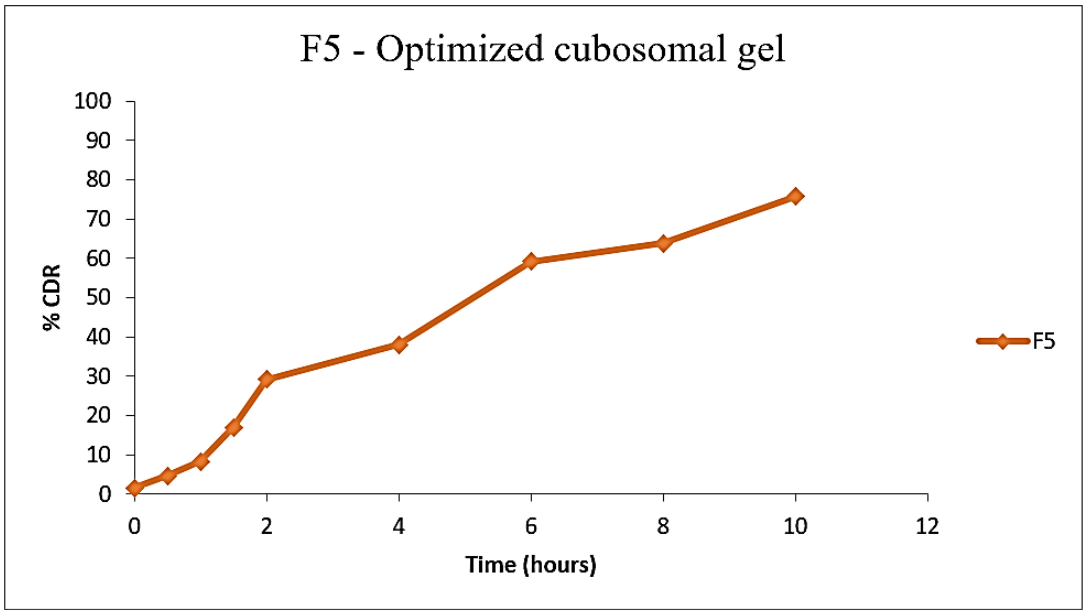

Figure 4: *Ex vivo* study of optimized formulation F5.

In vitro drug diffusion study

In vitro drug diffusion of Ibuprofen-loaded cubosomal gel was found to be 74.56%, indicating controlled drug release within 10 hr (Figure 3). The plain Ibuprofen gel drug released 68.57%. The drug diffusion of F5 gel was higher than that of conventional Ibuprofen gel. The optimized formulation F5 is released relatively swiftly at first, then at a lesser rate. The immediate quick release rate is attributable to free Ibuprofen on the surface of the cubosome particle, whereas drugs embedded within the particle core have been released over time. Furthermore, as a basic cubosome component, GMO may result in a decreased drug separation rate from the grease medium to the liquid medium when compared to pure medication, which may easily diffuse to the dissolving media. This finding corroborated the entrapment efficiency result.

Ex vivo studies

Ex vivo permeation testing on excised rat skin was carried out using the optimized formulation F5. After 10 hr, the release was determined to be 75.67±0.21 (Figure 4).

CONCLUSION

A notable attempt was tried to produce Ibuprofen-loaded cubosomes using PF-127 and GMO as polymers, which were then tested for compatibility and physical investigations. *In vitro* research demonstrated that cubosomal formulation F5 containing

7% GMO and 1.5% poloxamer 407 increased drug release, entrapment efficiency and stability. A cubosomal formulation that had been optimized was incorporated into the gel. *In vitro* drug diffusion and *ex vivo* permeation studies of optimized cubosomal gel (F5) revealed effective drug release compared to plain Ibuprofen gel. As a result, cubosomes represent a viable carrier for the ibuprofen transdermal drug delivery system.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

API: Active Pharmaceutical Ingredient; **COX-1:** Cyclooxygenase-1; **COX-2:** Cyclooxygenase-2; **cps:** Ceni-poise; **GMO:** Glyceryl Mono-Oleate; **HPLC:** High-Performance Liquid Chromatography; **kv:** Kilovolt; **λ_{max}:** Maximum Absorbance: **mL:** Millilitre; **min:** Minute; **mg:** Milligram; **NSAID:** Non-Steroidal Anti-Inflammatory Drug; **nm:** nanometer; **PF 127:** Pluronic F-127; **PDI:** Polydispersity Index; **Pvt Ltd:** Private Limited; **%EE:** Percent Entrapment Efficiency; **Rpm:** Revolutions Per Minute; **TEM:** Transmission Electron Microscopy; **USA:** United States of America.

SUMMARY

Ibuprofen-loaded Cubosomal Nanoformulation was prepared using a top-down approach by varying Glyceryl Mono-Oleate (GMO) and Polaxomer 407 (PF 127). The prepared cubosomal nanoformulations were subjected to characterization such as Poly Dispersibility Index, Particle Size and Entrapment Efficiency. The optimized formulation of Ibuprofen-loaded Cubosomes was incorporated in Carbopol 940 (1%) gel base. The gel formulations were evaluated for pH, viscosity, spreadability, *in vitro* drug diffusion through a cellophane membrane and *ex vivo* diffusion studies using rat skin. A 3^2 factorial design was utilized for formulation optimization. The optimized cubosomal nanoformulation (F5) produced particles with an average particle size of 150.7 nm and PDI of <1, zeta potential of -29mV and %drug entrapment efficiency of 74.36±0.66%. The formulated Cubosomal Gel revealed a neutral pH value with a viscosity of 1123±0.45cps, 75% *in vitro* drug diffusion and 78.6% *ex vivo* drug diffusion.pH, viscosity, spreadability, drug release and stability studies were performed on the Cubosomal gel formulation. The optimized Formulation (F5) performed better in terms of pH, viscosity, spreadability and drug release percentage. *In vitro* and *ex vivo* studies shows that Ibuprofen-loaded Cubosomal gel releases the drug more slowly than plain formulated Ibuprofen Gel. The formulated Cubosomal Gel also showed no significant change in physical.

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